Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	February 13, 2013
To:	Ruyi He, MD, Medical Officer Team Leader Division of Gastroenterology and Inborn Errors, Products (DGIEP), Office of New Drugs (OND) Joyce Korvick, MD, MPH Deputy Director of Safety, DGIEP, OND Donna Griebel, MD Director, DGIEP, OND
Reviewer(s):	Christian Cao, MPAS, PA-C, Safety Evaluator Division of Pharmacovigilance-1 (DPV-1), Office of Safety and Epidemiology (OSE) Ali Niak, MD Medical Officer, DPV-1, OSE Ethan Hausman, Medical Officer, DPV-1, OSE
Team Leaders:	Ann Corken Mackey, RPh, MPH, Safety Evaluator Team Leader, DPV-1, OSE Shewit Bezabeh MD, MPH Medical Officer Team Leader, DPV-2, OSE
Division Director:	Linda Scarazzini, MD, RPh DPV-1, OSE
Product Name(s):	Zofran (ondansetron hydrochloride), Zofran and Dextrose in Plastic Container (ondansetron hydrochloride), Zofran ODT (ondansetron), Zuplenz (ondansetron), Kytril (granisetron hydrochloride), Sancuso (granisetron), Aloxi (palonosetron hydrochloride), Anzemet (dolasetron mesylate)
Subject:	Serotonin Syndrome
Application Type/Number:	NDA 020007, 020103, 020605, 020403, 020781, 022524, 020239, 020305, 021238, 022198, 021372, 020623, 020624
Applicant/Sponsor:	GlaxoSmithKline, Vestiq Pharmaceuticals, Hoffmann La Roche Inc., Prostrakan Inc., Helsinn Healthcare SA, Sanofi Aventis US LLC
OSE RCM #:	2012-1186

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates the risk of developing serotonin syndrome (SS) with the use of a 5-HT_3 receptor antagonist (ondansetron, granisetron, palonosetron, and dolasetron) when used alone or when used in combination with other serotonergic drugs. These findings will help formulate the final recommendation to the Advisory Committee evaluating the pediatric postmarket adverse events for Kytril (granisetron hydrochloride) in March 2013. A concurrent pediatric safety review identified SS as a potential unlabeled adverse drug reaction related to Kytril.

SS is a potentially life-threatening condition that is most commonly related to drug use. Its diagnosis is often missed due to unfamiliarity with the diagnostic criteria and the pharmacology of the potential offending drugs. When drug-associated SS is recognized, the management is discontinuation of the offending drug, or drugs, and provision of supportive care.

Since approval of the first 5-HT_3 receptor antagonist, Zofran (ondansetron), in 1991, the use of this class of medications as antiemetic agents has become widespread during chemotherapy and postsurgical situations in adult and pediatric patients. Ondansetron products accounted for over 99% of the serotonin 5-HT_3 receptor antagonist utilization for years 2008 to 2012.

A search of the FAERS database and medical literature identified 39 cases of serotonin syndrome related to use of ondansetron (n = 29), granisetron (n = 7), dolasetron (n = 2), and ondansetron and granisetron in combination (n = 1). There were no cases found for palonosetron. Most cases involved use of a concomitant serotonergic agent. Often, the patients were taking the concomitant serotonergic drug chronically and developed SS after exposure to the 5-HT_3 receptor antagonist. There were 3 deaths. Two deaths were related to SS and 1 death was possibly related to the patient's underlying medical condition. Sex and age of the patients did not appear to be factors in the development of SS. There were 7 pediatric cases of which two were related to accidental overdoses of ondansetron, as a single agent.

Based on the cases reviewed and medical literature suggesting several biologically plausible explanations, there is potential for developing SS with the 5-HT_3 receptor antagonist drug-class when used alone or with other serotonergic drugs in both sexes and in all age groups.

Due to the seriousness of SS, as reflected in our case series, we suggest this information be placed in the labeling for all 5-HT_3 receptor antagonists. In addition, we recommend updating the Overdose sections to include information from the 2 pediatric overdoses of ondansetron leading to SS.

1 INTRODUCTION

1.1 BACKGROUND

The purpose of this review is to evaluate the risk of developing SS (SS) with the use of a 5-HT_3 receptor antagonist alone or with other serotonergic drugs. The findings from this review will help formulate the final recommendation to the Advisory Committee evaluating the pediatric postmarket adverse events for Kytril (granisetron hydrochloride) in March 2013. A pediatric safety review had identified SS as a potential unlabeled adverse drug reaction related to Kytril.

A potential signal was initially identified in December 2011 during routine monitoring when a case of SS related to an overdose of ondansetron was received to the FAERS database. The signal was intensified when the World Health Organization (WHO) published a case series in the March 2012 *SIGNAL*[1] issue and then subsequently in their *WHO Pharmaceutical Newsletter*[2] in June 2012 their review of Ondansetron and SS. They concluded, "ondansetron may contribute to the development of SS in susceptible patients concomitantly receiving other drugs affecting the serotonin system" and that "patient safety would be served if it was considered to also be mentioned in the product labeling."

Since approval of the first 5-HT_3 receptor antagonist, Zofran (ondansetron), in 1991, the use of this class of medications as antiemetic agents has become widespread during chemotherapy and postsurgical situations. The mechanism of action for the 5-HT_3 receptor antagonists has been well documented since the 1950s when the existence of two serotonin receptor subtypes, the M (5-HT_3 receptor) and D receptors, were proposed.[3] Most 5-HT_3 receptor antagonists are rapidly absorbed and easily penetrate the blood-brain barrier. They act centrally on the chemoreceptor trigger zone of the area postrema and peripherally at the vagus nerve terminals in the small intestine preventing signals to the central nervous system (CNS) to prevent nausea and vomiting.

Drug-associated SS is a potentially life-threatening condition caused by an increase in intrasynaptic serotonin, typically at the 5-HT_{1A} or 5-HT_{2A} receptors in the CNS[4], and is more common than a similar syndrome cause by serotonergic carcinoid tumors. The condition is thought to be related to prescription or recreational drug exposures, though patients with serotonergic carcinoid syndrome may present with a similar physical findings. The signs and symptoms for SS include 1) mental status alterations, 2) autonomic signs (e.g., shivering, sweating, and temperature elevation) and 3) neuromuscular changes, (e.g., tremor, and paralysis). This clinical triad is the basis of the Sternbach diagnostic criteria published in 1991.[5] In the context of an appropriate history and physical examination, the Hunter Criteria published in 2005 is 84% sensitive and 97% specific and is the favored diagnostic tool for SS.[6] In order to fulfill the Hunter Criteria, a serotonergic agent must have been administered recently within the past 5 weeks and meet one of the following conditions:

- spontaneous clonus
- inducible clonus PLUS agitation or diaphoresis
- ocular clonus PLUS agitation or diaphoresis
- Tremor PLUS hyperreflexia
- hypertonia PLUS fever (> 38°C) PLUS ocular clonus or inducible clonus

There are three principles to the management of drug associated-SS: 1) discontinuation of all serotonergic agents, 2) supportive care and 3) cyproheptadine, a nonspecific 5-HT_{1A} and 5-HT_{2A} receptor antagonist. Severe cases of SS require management in the intensive care unit (ICU). Typically, the prognosis is favorable, but failure to diagnose and treat SS can lead to

complications including severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, cardiac arrhythmias, acute respiratory distress syndrome (ARDS), and possibly death.[5]

1.2 REGULATORY HISTORY

The 5-HT_3 receptor antagonist drug-class consists of four primary drugs Zofran, Kytril, Aloxi and Anzemet. Zofran is the oldest with its marketing approval in 1991. FDA approvals of the other drugs in the class were Kytril in 1994, Anzemet in 1997 and Aloxi in 2003. Each drug may have several approved indications and routes of administration. Ondansetron, granisetron and dolasetron are approved for use in pediatric patients. Palonosetron has not been studied in children. Table 1 summarizes the regulatory history of the 5-HT_3 receptor antagonists.

Table 1. 5-HT_3 Receptor Antagonist Regulatory Summary

Product Name	Active ingredient	NDA	Initial Approval	Indication(s)*	Route(s)	Pediatric Approval
Zofran, Zofran and Dextrose in Plastic Container, Zofran ODT, Zuplenz	Ondansetron	020007 020103 020605 020403 020781 022524	1991	CINV, RINC, PONV	IV, PO Tab, PO Soln	Yes
Kytril, Sancuso	Granisetron	020239 020305 021238 022198	1994	CINV, PONV	IV, PO Tab, Transdermal	Yes
Anzemet	Dolasetron	020623 020624	1997	CINV, PONV	IV, PO Tab	Yes
Aloxi	Palonosetron	021372 022233	2003	CINV, PONV	IV, PO Cap	No

*CINV = chemotherapy induced nausea and vomiting, RINC = radiation therapy induced nausea and vomiting, PONV = post-operative nausea and vomiting

1.3 PRODUCT LABELING

While the risk of SS is not specified in labeling of any 5-HT_3 receptor antagonist in this review, each drug is labeled for signs and symptoms that are compatible with SS (e.g., fever, chills, sweating).

An overdose of Anzemet (6.3 to 12.6 times the recommended human dose based on body surface area) was reported to be lethal in mice with symptoms including tremors, depression and convulsions. Similarly, overdoses with Aloxi were also lethal in mice with signs of toxicity including convulsions, gasping, pallor, cyanosis and collapse. Please see Table 2 for specific labeled events.

Table 2. Selected AE for 5-HT_3 Receptor Antagonist

Product	Labeled AE that are associated with SS (Label section)*		Labeled for Extrapyramidal Reaction (Label section)
Zofran	• diarrhea (AR, 6.1) • fever (AR, 6.1) • hypotension (AR, 6.1, OD)	• grand mal seizure (AR, 6.1) • flushing (AR, 6.2) • oculogyric crisis (AR,	Yes (AR, 6.1)

Table 2. Selected AE for 5-HT_3 Receptor Antagonist			
Product	**Labeled AE that are associated with SS (Label section)***		**Labeled for Extrapyramidal Reaction (Label section)**
	• tachycardia (AR, 6.1)	6.2)	
Zofran ODT	• diarrhea (AR) • grand mal seizure (AR) • pyrexia (AR) • anxiety/agitation (AR)	• shivers (AR) • hypotension (AR, OD) • flushing (AR) • oculogyric crisis (AR)	Yes (AR)
Zuplenz	• diarrhea (AR, 6.1) • pyrexia (AR, 6.1) • hypotension (AR, 6.2, OD) • tachycardia (AR, 6.1)	• grand mal seizure (AR, 6.1) • anxiety/agitation (AR, 6.1) • flushing (AR, 6.2) • oculogyric crisis (AR, 6.2)	Yes (AR, 6.1)
Kytril	• hypertension (AR, 6.1) • hypotension (AR, 6.1) • anxiety (AR, 6.1) • agitation (AR, 6.1)	• CNS stimulation (AR, 6.1) • insomnia (AR, 6.1) • fever (AR, 6.1) • diarrhea (AR, 6.1)	Yes (AR, 6.1)
Sancuso	• diarrhea (AR, 6.1) • hypertension (AR, 6.1) • hypotension (AR, 6.1) • syncope (AR, 6.1)	• insomnia (AR, 6.1) • anxiety (AR, 6.1) • fever (AR, 6.1)	No
Anzemet	• chills/shivering (AR) • hypotension (AR) • flushing (AR) • agitation (AR) • anxiety (AR)	• abnormal dreaming (AR) • tremors (OD) • depression (OD) • convulsion (OD)	No
Aloxi	• diarrhea (AR, 6.1) • insomnia (AR, 6.1) • hypotension (AR, 6.1) • hypertension (AR, 6.1) • dry mouth (AR, 6.1) • metabolic acidosis (AR, 6.1) • fever (AR, 6.1)	• hot flashes (AR, 6.1) • anorexia (AR, 6.1) • anxiety (AR, 6.1) • chills (AR, 6.2) • convulsions (OD) • pallor (OD)	No

*AR = Adverse Reactions, OD = Overdosage

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

Inclusion Criteria

To be included as a case of SS for review, the following criteria must be met:

a) The case must be coded with the MedDRA preferred term (PT) "serotonin syndrome"

OR

The case meets the Hunter Criteria

- spontaneous clonus
- inducible clonus PLUS agitation or diaphoresis
- ocular clonus PLUS agitation or diaphoresis
- Tremor PLUS hyperreflexia
- hypertonia PLUS fever (> 38°C) PLUS ocular clonus or inducible clonus

b) A serotonergic agent must be a suspect or concomitant drug listed in the adverse event report

Exclusion Criteria

a) Cases of neuroleptic malignant syndrome (NMS) must be excluded. NMS is usually marked by a slow onset and is associated with the use of dopamine antagonists.

b) Other diagnoses that may have similar clinical manifestations as SS (such as hyperthyroidism, which may also produce tachycardia, diarrhea, tremor, etc.) must be excluded.

Cases with the clinical triad of mental status changes, autonomic symptoms and neuromuscular symptoms are also considered depending on the cases outcome.

2.2 FAERS SEARCH STRATEGY

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 2.

Table 2. FAERS Search Strategy*

Date of search	November 29, 2012
Time period of search	January 1, 1965^ - November 28, 2012
Product Terms	**Product Active Ingredient:** DOLASETRON; DOLASETRON MESYLATE; GRANISETRON;GRANISETRON HYDROCHLORIDE; GRANISETRON\GRANISETRON HYDROCHLORIDE; ONDANSETRON;ONDANSETRON HYDROCHLORIDE; ONDANSETRON\ONDANSETRON HYDROCHLORIDE; PALONOSETRON; PALONOSETRON HYDROCHLORIDE **Product Name:** DOLASETRON; DOLASETRON MESYLATE; ONDANSETRON AND DEXTROSE; ONDANSETRON HYDROCHLORIDE; ONDANSETRON HYDROCHLORIDE AND DEXTROSE; PALONOSETRON; PALONOSETRON HYDROCHLORIDE; GRANISOL; KYTRIL; SANCUSO; ANZEMET; ALOXI; ZOFRAN; ZOFRAN ODT; ZUPLENZ
MedDRA Search Terms	**PT:** CLONUS; MYOCLONUS; AGITATION; HYPERHIDROSIS; HYPERREFLEXIA; HYPERTONIA; HYPERPYREXIA; PYREXIA **HLT:** TREMOR (EXCL CONGENITAL) **SOC:** EYE DISORDERS
Narrative Search	clonus, myoclonus

* See Appendix A for description of the FAERS database.
^ All reports in FAERS

2.3 DRUG UTILIZATION

The Division of Epidemiology II (DEPI II) completed a drug use analysis of the four 5-HT_3 receptor antagonist ondansetron, granisetron, palonosetron and dolasetron.[7] Their review analyzed data for hospital inpatient and outpatient emergency room (ER) patients (0-16, 17-64, and 65+ years) from years 2007 through March 31, 2012 retrieved from the IMS Inpatient HealthCare Utilization System (IHCarUS) database.

2.4 LITERATURE SEARCH

The medical literature was searched with the strategy described in Table 3.

Table 3. Literature Search Strategy

Date of search	December 6, 2012
Database	PubMed
Search Terms	("serotonin syndrome" AND ondansetron) OR ("serotonin syndrome" AND granisetron) OR ("serotonin syndrome" AND dolasetron) OR ("serotonin syndrome" AND palonosetron)
Years included in search	No limitations

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 137 reports. After applying the case definition in Section 2 and accounting for duplicate reports, 39 cases met the case definition and were included in the case series (see Figure 1).

Figure 1. FAERS Case Selection

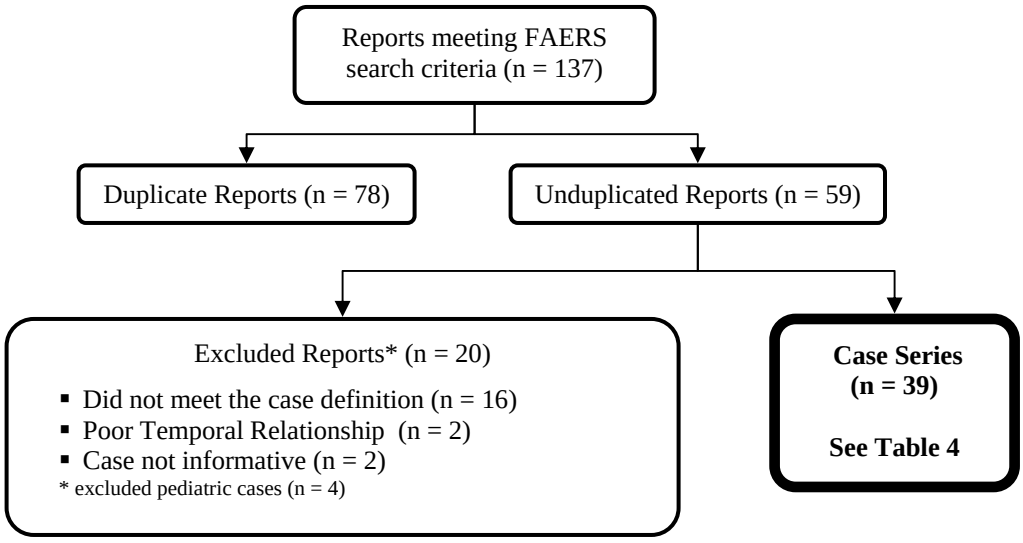

Table 4 summarizes the 39 FAERS cases of SS reported with the 5-HT_3 receptor antagonists for this case series.

Appendix B lists all the FAERS case numbers and Manufacturer Control numbers for the 39 cases in this case series.

Table 4. Descriptive characteristics of SS reported with 5-HT_3 receptor antagonists use, received by FDA from January 1, 1965 - November 28, 2012 (N=39)

5-HT3 receptor antagonist(s)	Ondansetron (n = 29)	
	• with concomitant serotonergic drug(s)	20
	• concomitant serotonergic drug(s) not reported	9
	Granisetron (n = 7)	
	• with concomitant serotonergic drug(s)	4
	• concomitant serotonergic drug(s) not reported	3
	Dolasetron (n = 2)	
	• with concomitant serotonergic drug(s)	2
	• concomitant serotonergic drug(s) not reported	0
	Ondansetron + Granisetron (n = 1)	
	• with concomitant serotonergic drug(s)	0
	• concomitant serotonergic drug(s) not reported	1
	Palonosetron (n = 0)	
Indication/Reason for exposure (n = 32)	PONV*	15
	CINV*	11
	Nausea/vomiting***	4
	Accidental Ingestion	2
Concomitant Serotonergic Agent** (n = 26)	Ondansetron (n = 20)	
	fentanyl	8
	mirtazapine	4
	paroxetine	4
	methylene blue	3
	tramadol	3
	citalopram	2
	duloxetine	2
	bupropion	1
	escitolapram	1
	granisetron	1
	lithium	1
	phenelzine sulphate	1
	sertraline	1
	venlafaxine	1
	Granisetron (n = 4)	
	venlafaxine	2
	"an antidepressant"	1
	fentanyl	1
	methylene blue	1
	ondansetron	1
	sufentanil	1
	Dolasetron (n = 2)	
	sertraline	2

Age (n = 33) Pediatric Cases (n = 7)	Mean Median Range	44 47 1-80
	< 1 years 1-2 years 3-6 years 6-16 years 16-64 years ≥ 65 years	0 2 0 5 17 9
Sex (n = 37)	Male Female	20 17
Report Year	1997 1998 1999 2001 2002 2003 2004 2005 2006 2008 2009 2010 2011 2012	1 1 1 2 3 1 1 1 3 2 4 4 4 10
Report Type	Expedited Periodic Direct	37 1 1
Outcomes (n = 37)	Death Hospitalization Life Threatening Other	3 19 3 12

*CINV = chemotherapy induced nausea and vomiting, PONV = post-operative nausea and vomiting
**A case may report multiple concomitant drugs
***Off-label indication as reported in the MedWatch form

Best Representative Case

Case 7055030 (69 y/o Female, 2009): This is a case from Great Britain of a 69 years-old female who suffered SS after receiving ondansetron hydrochloride for PONV related to knee replacement surgery. She also received oxycontin after the surgery. She did not receive general anesthesia; only a regional block was used for the knee arthroplasty. Her chronic medications were phenelzine sulphate, orlistat, ramipril, amiloride HCL and diazepam. Within hours of ondansetron exposure, the patient exhibited drowsiness, confusion, agitation, hallucination, hypertension (BP 160-180 mmHg systolic) and fever (T 38C). A diagnosis of SS was made and both ondansetron and oxycontin were discontinued. Aside from supportive care, she required chlorpromazine to manage her agitation. She returned to baseline on the fifth day post-operation with no reported sequelae.

Reviewer Comment: *This is a probable case representing the potential risk of developing SS when a 5-HT_3 receptor antagonist is given to a patient who chronically takes a serotonergic agent; in this case, phenelzine, a monoamine oxidase inhibitor (MAOI). The patient did not receive any other drug known to precipitate SS. The presentation of the symptoms within hours of ondansetron exposure supports a temporal relationship between the drug and event.*

Death Cases (n = 3)

Case 3120931 (30 y/o Male, 1998): This is a domestic case of a 30-year-old male with malignant melanoma who died within 1 day of receiving ondansetron IV, dexamethasone, lorazepam, cisplatin, carmustine, dacarbazine, and tamoxifen for chemotherapy. Fentanyl was also listed as a concomitant medication, but not given at the chemotherapy session. The patient was given ondansetron PO in addition to use as an outpatient for nausea and vomiting. He exhibited confusion at discharge from his chemotherapy session. This worsened in the evening and he was found comatose the next morning. Other reported symptoms were agitation and mydriasis. According to the attending physician, the patient was exhibiting signs of "autonomic overdrive." He suffered a seizure later that day and died. The cause of death was reported to be due to cerebral necrosis secondary to status epilepticus. Evaluation for metastasis of the melanoma to the brain including an autopsy was negative.

Reviewer Comment: *This is a possible case of SS related to use of ondansetron concomitantly with fentanyl. Fentanyl is a direct serotonin receptor agonist and is a known drug that can precipitate SS. The patient started exhibiting confusion, a possible early sign of serotonin syndrome, within hours after ondansetron exposure; however no intervention was taken at that time. The next day he was found comatose and he subsequently died. It was not reported whether the patient took additional doses of ondansetron and/or fentanyl after discharge from the chemotherapy. It is also not reported whether the patient took fentanyl chronically.*

Case 7370213 (69 y/o Female, 2010): A 69-year-old female from the Netherlands died as a result of SS after receiving Kytril (granisetron), Sufenta (sufentanil citrate), Methylene Blue (methylthioninium chloride), and Droperidol. The SS developed after she underwent surgery for an unreported indication, but was initially diagnosed as malignant neuroleptic syndrome. The diagnosis of SS was made after the patient's death and only after reviewing the medical literature. She was taking Effexor (venlafaxine) XR 75 mg BID chronically for the previous 11 months.

Reviewer Comment*: This is a probable case of serotonin syndrome related to use of multiple serotonergic drugs: granisetron, sufentanil, methylene blue, and venlafaxine.*

Case 3681649 (11 y/o Female, 2001): An 11-year-old female developed SS (confusion with visual hallucination, marked anxiety, tremulousness, ataxia and myoclonus) approximately 2 weeks after exposure to granisetron, busulfan, cyclophosphamide, antibacterial, antifungal, antiviral antibiotics, cyclosporine and fentanyl. Onset of SS coincided with development of renal and hepatic impairment secondary to veno-occlusive disease related to a bone-marrow transplant. The SS resolved with discontinuation of granisetron and fentanyl, but she died 6 weeks later due to progressive renal and hepatic failure.

Reviewer Comment: *This is a possible case of SS related to use of granisetron and fentanyl. The onset of the SS developed several weeks after drug exposure, and after development of hepato-renal impairment, which may possibly lead to decreased metabolism or excretion of one or both drugs. It is unknown whether the SS had any contribution to the patient's death.*

Overdose/Accidental Exposure Cases

Case 5085758 (1 y/o Male, 2009): This is a domestic case from a literature report of a 12-month-old boy who suffered SS due to inadvertent ingestion of 56-64 mg of ondansetron. He became somnolent and developed myoclonic movements in his extremities within 20 minutes of taking the drug. Other diagnostic features of SS included tachycardia (HR 175 BPM), tachypnea (RR 35 breaths/min), hypertension (BP 123/74 mmHg), depressed mental status, horizontal nystagmus (ocular clonus), hyperreflexia, facial flushing, mydriasis, and diaphoresis. The SS was complicated by tonic-clonic seizure when his oxygenation desaturated. Treatment and intervention included intubation, administration of activated charcoal and supportive care in the ICU. The patient returned to baseline and was discharged from the hospital after 48 hours.

Reviewer Comment: *This is a case of ondansetron-related SS in a pediatric patient with a clear temporal relationship. This case was not confounded by any concomitant drug or medical condition. It is not known if the differences in pediatric metabolism of ondansetron or the immaturity of the infant's nervous system contributed to this adverse drug reaction.*

3.2 DRUG UTILIZATION[7]

- In the hospital inpatient and outpatient ER setting, the total number of discharges and patients billed for serotonin 5-HT3 receptor antagonists increased from 11.4 million discharges and 9.6 million patients in year 2007 to 26.2 million discharges and 20.3 million patients in year 2011.
- Ondansetron products accounted for over 99% of the serotonin 5-HT3 receptor antagonist utilization for years 2008 to 2012.
- For ondansetron products, approximately 11% (2.1 million) of patients were aged 0-16 years; elderly patients (65+ years) accounted for 21% (4.3 million) of patients in year 2011.
- The majority of patients billed for serotonin 5-HT3 receptor antagonists were females at 62% of total patients compared to males at 37% of total patients.

3.3 LITERATURE SEARCH

The literature search based on the parameters outlined in Table 3 retrieved 6 articles 5 of which were also cases found in the FAERS database. The sixth article was a report on amantadine withdrawal and neuroleptic malignant syndrome. There were no additional cases of SS related to a 5-HT_3 receptor antagonist found in PubMed.

4 DISCUSSION

There are several biologically plausible explanations for how 5-HT_3 receptor antagonists may contribute to the development of SS. Altman et al proposed in their article (case# 8431466) that ondansetron may increase the systemic availability of serotonin by occupying the 5-HT_3 receptors and consequently lead to stimulation of other serotonin receptor subtypes (e.g. 5-HT_{1a} and 5-HT_{2a}) by endogenous serotonin.[8] In order for Altman's hypothesis to be true, there would have to be a concomitant serotonergic agent for SS to develop. Our case series appears to support Altman's hypothesis; 26 of 39 cases (66%) reported concomitant use of one or more serotonergic agents. This hypothesis, however, would not explain how a 5-HT_3 receptor antagonist alone might contribute to SS as in the 2 cases of overdose by otherwise healthy 1-year-old infants (case# 5085758 and 8277817). Alternative explanations may be that 5-HT_{1a} and

5-HT_{2a} receptors are not solely responsible for SS, or that 5-HT_3 receptor antagonists may bind to and activate other serotonin receptors as agonists when 5-HT_3 receptors are saturated. Review of the literature supports these alternative hypotheses; Culy et al reported that ondansetron also binds to 5-HT_{1B} and 5-HT_{1C} receptors[9]and Boyer noted that no single serotonin receptor subtype appears to be responsible for the development of SS.[6]

Patient sex and age did not appear to be factors in the development of SS. There was an even distribution for gender and a broad age range in our case series. Twenty reports of SS were in males and 17 reports for females. The age distribution was from 1-year-old to 80-year-old, which corresponds to the epidemiology of SS for all other serotonergic drugs.[6]

Our review suggests that the potential for SS exists across all 5-HT_3 receptor antagonists. There were more cases reported with ondansetron exposure; however, given the inherent limitations of estimating comparative risk with uncontrolled postmarket data, no estimate of relative risk across the drug class can be made. Additionally, the greater number of cases of ondansetron and SS may be attributable to greater market penetration of this drug which is consistent with our drug use data which shows that ondansetron has > 99% market share.

Additionally, since extrapyramidal reactions are labeled adverse drug reactions for several of the drugs in the class, and since symptoms extrapyramidal syndrome overlap with symptoms of SS, there may be under-reporting of SS events. Furthermore, cases of SS misclassified as extrapyramidal reactions, and may therefore be relegated to periodic reports because extrapyramidal reactions are labeled (15-day reporting is not required per 21 CFR 314.80 for labeled events). To explore this hypothesis we performed an additional search the FAERS database for reports of extrapyramidal reactions. There are 129 cases coded with the PT extrapyramidal disorder or tardive dyskinesia for dolasetron, granisetron and ondansetron (zero cases for palonosetron). Seven of these cases also were found with our search strategy for SS. Nearly 35 percent of the cases were periodic reports and 35 cases reported concomitant use of a serotonergic agent. Given the overlapping symptoms between the two conditions, it is possible that some of these cases may have been SS, although were classified and reported as extrapyramidal reactions.

Increasing use of drugs that act on the serotonergic system may increased potential for patients to develop SS especially with concomitant medications.[10] Our case series support the risk of developing SS when a 5-HT_3 receptor antagonist is used concomitantly with another serotonergic agent. More than 2/3 of the patients (n = 26) in this review were exposed to a concomitant serotonergic agent. Furthermore, there was concomitant serotonergic drug exposure in all 3 deaths.

Because of the under-recognition of SS and its possible lethality, it is important that clinicians are aware of the risk of developing SS with the use of any 5-HT_3 receptor antagonist alone or with other serotonergic drugs. For example, Mackay et al's survey data reported 41 of 45 (85%) of physicians caring patients with serotonin syndrome diagnosed by third party questionnaire were unaware that SS exists as a diagnosis.[11] Lastly, in one of the death cases in our case series, the physician did not recognize that the patient may have had SS until after the patient died when he reviewed the medical literature.

5 CONCLUSION

Based on the information reviewed, there is potential for developing SS with the 5-HT_3 receptor antagonist drug-class when used alone, and when used concomitantly with other serotonergic drugs in both sexes and in all age groups. In addition to the quality cases of SS from the FAERS database demonstrating temporal relationship, the literature also suggests that there may be biologic plausibility of SS with the 5-HT_3 receptor antagonist drug class.

6 RECOMMENDATIONS

Due to the seriousness of SS, as reflected in our case series, we suggest this information be placed in the labeling for all 5-HT_3 receptor antagonists. In addition, we recommend updating the Overdose sections to include information from the 2 pediatric overdoses of ondansetron leading to SS.

7 REFERENCES

1. WHO SIGNAL. March 2012.
2. WHO Pharmaceuticals Newsletter. No. 3, 2012.
3. Gaddum JH and ZP Picarelli. Two kinds of tryptamine receptor. British Journal of Pharmacology and Chemo-therapy.1957;12(3):323–328.
4. Sternbach H. The SS. Am J Psychiatry 1991 ; 148 : 705 -13.
5. Mason PJ, Morris VA, Balcezak TJ. SS. Presentation of 2 cases and review of the literature. Medicine (Baltimore). 2000; 79(4):201-9.
6. Boyer EW and Shannon M; The serotonin syndrome; NEJM 2005;352:1112
7. Greene PA. Drug Use Review: Drug utilization for antiemetic agents (serotonin 5-HT3 receptor antagonists). RCM #2012-1199. July 17, 2012.
8. Altman, C. S., & Jahangiri, M. F. (2010). SS in the perioperative period. Anesthesia & Analgesia, 110(2), 526-528.
9. Culy, C. R., Bhana, N., & Plosker, G. L. (2001). Ondansetron: a review of its use as an antiemetic in children. Pediatric Drugs, 3(6), 441-479.
10. Jones, D., & Story, D. A. (2005). SS and the anaesthetist. Anaesth Intensive Care, 33(2), 181-187.
11. Mackay, F. J., Dunn, N. R., & Mann, R. D. (1999). Antidepressants and the SS in general practice. The British Journal of General Practice, 49(448), 871.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS CASE NUMBERS AND MANUFACTURER CONTROL NUMBERS

FAERS Case Numbers	Version Number	Manufacturer Control Numbers
3120931	2	A0059948
3193389	2	1999000154-1
3653771	2	B0105115A
3678414	2	A0152415A
3681649	1	2001015644-1
3785067	1	A0163667A
3821543	1	A214487
4029073	1	B0311559A
5085758	2	57831
5513500	1	960177691
5673132	1	FR-GLAXOSMITHKLINE-B0350288A
5881482	2	GB-GLAXOSMITHKLINE-B0393288A
6019704	1	
6055496	1	US-AVENTIS-200614691US
6066991	1	CA-GLAXOSMITHKLINE-A0609182A
6073032	3	GB-GLAXOSMITHKLINE-B0428345A
6549316	1	2008AP000216
6662359	2	B0524398A
6744903	1	B0534412A
6948736	1	US-ASTRAZENECA-2009AC00860
7050566	2	NZ-NAPPMUNDI-USA-2009-0039097
7055030	1	B0583172A
7370213	1	NL-WYE-G06029410
7645367	1	B0680805A
7691266	2	ZA-ROCHE-744171
7847814	1	CA-ROCHE-763274
8109018	1	FR-GLAXOSMITHKLINE-B0740643A
8143298	2	2011SP039169
8277817	1	US-PFIZER INC-2011294857
8431466	1	US-COVIDIEN/TYCO HEALTHCARE/MALLINCKRODT-T201200648
8437974	1	09-AUR-10543
8468199	1	PL-GLAXOSMITHKLINE-B0789485A
8474606	1	DE-TEVA-327610GER
8569779	3	US-PFIZER INC-2012116877
8654609	1	FR-ROCHE-1082579
8675657	1	PHHY2012PL061187
8801153	1	ZA-ROCHE-1130013
8818583	2	GB-PFIZER INC-2012236183
8917754	1	US-MYLANLABS-2012S1023492

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTIAN T CAO
02/13/2013

ALI NIAK
02/13/2013

ETHAN D HAUSMAN
02/13/2013

ANN MACKEY
02/13/2013

SHEWIT BEZABEH
02/13/2013

LINDA J SCARAZZINI
02/13/2013